A -2
2/7/94

US EPA RECORDS CENTER REGION 5

||||||||||||||||||||||||||||||||||||||||||
471852

MEMORANDUM

DATE: February 7, 1994

SUBJECT: Systemic Toxicity and/or Carcinogenicity for Antimony (CASRN 7440-36-0) and Cobalt (CASRN 7440-48-4) (Albion Sheridan Township Landfill/Albion, MI)

FROM: Joan S. Dollarhide
              Director
              Superfund Health Risk Technical Support Center
              Chemical Mixtures Assessment Branch

TO: Erin Moran
              U.S. EPA
              Region V

        This memorandum responds to your request for any toxicity information available for antimony and cobalt for use at the Albion Sheridan Township Landfill, Albion, MI.

        Attached please find the following information:

- **Attachment I.**   **Risk Assessment Issue Paper for: Summary of Toxicity and Carcinogenicity of Antimony (CASRN 7440-36-0)**
                        (It should be noted that this is an older paper and has not been updated.)

- **Attachment II.**   **Risk Assessment Issue Paper for: Provisional RfD for Cobalt (CASRN 7440-48-4)**

        Please feel free to contact the Superfund Technical Support Center at (513) 569-7300 if you need additional assistance.

Attachments

cc: B. Farrell (WW Engineering and Science)

Attachment I.

Risk Assessment Issue Paper for:
Summary of Toxicity and Carcinogenicity of Antimony (CASRN 7440-36-0)

Antimony (Sb) is a naturally occurring element found as various salts in seawater, surface water, soils and sediments. Antimony concentrations in the earth's crust are approximately 0.2 to 1.0 mg/kg (Rompp, 1979). More than half of the naturally occurring antimony in sediments is bound to extractable iron and aluminum (Crecelius et al., 1975). Antimony III and V forms and methyl antimony compounds have been shown to exist in natural waters. Ragaini et al. (1977) reported that lead smelting operations in the Kellog Valley of Idaho resulted in soil antimony concentrations ranging from 5 to 260 μg/g. Also, reports indicated that 2 to 3 times higher than background levels have been reported in Puget Sound sediments within 8 to 15 kilometers from a copper smelting operation.

Antimony is not readily absorbed from the gastrointestinal tract. Approximately 15% of the administered dose of radioactive antimony was estimated to be absorbed from the rat intestine (Moskalev, 1959). Gerber et al., (1982) indicated that concentrations of ^{125}Sb in lung, bone, ovaries and uterus ranged from 0.085 to 0.2% when given in food to pregnant BALB/C mice. Available human data indicated that blood, liver, skeletal muscle and urine are four major compartments of distribution for antimony following single intravenous injection of radioactive potassium antimony tartrate (Rowland, 1971). Otto and Maren (1950) reviewed the routes of excretion of parenterally administered antimony in different species and humans. Trivalent antimony was excreted via the feces and urine whereas the pentavalent form was primarily excreted in the urine.

HEALTH EFFECTS

Schroeder et al., (1946) reported the effect of antimony III and antimony V compounds on the electrocardiogram (EKG) of human patients being treated for schistosomiasis. Sodium antimony compound (Stibophen NF or Fuadin) was given intramuscularly and potassium antimony tartrate was given intravenously daily or on alternate days for about one month; average daily doses ranged from 0.24 to 0.89 mg antimony/kg/day. Examination of EKGs from 100 patients were not indicative of cardiac damage or serious impairment of cardiac function. Death, however, was reported in two patients (4 year old girl and 70 year old woman) treated parenterally with about 2 mg antimony III/kg for parasitic infestations. Both patients died shortly after the second dose (Rugemalila, 1980).

Chulay et al., (1985) observed EKG changes in 59 patients dosed orally with 10, 20, 40 and 60 mg/kg/day antimony V for leishmaniasis. Dose-related increases in EKG abnormalities were found following 65 courses of antimony treatment which lasted for four months. Furthermore, the frequency of EKG abnormalities increased with the duration of treatment. Potkonjak and Pavlovich (1983) reported clinical findings for 51 male workers (ages 31 to 54) exposed for 9 to 31 years to dust containing a mixture of antimony III and antimony V in an antimony smelting plant. Characteristic changes observed were categorized as pneumoconiosis simplex or antimoniosis. The symptoms included chronic coughing, conjunctivitis, orange-colored staining of frontal tooth surface, chronic bronchitis, chronic emphysema and pleural adhesions. Antimony dermatitis, characterized by vesicular or pustular lesions, was seen in more than half the exposed workers. Reports of the effects of antimony on reproductive/developmental effects in humans are equivocal and limited.

U.S. EPA REGULATORY DECISIONS

The U.S. EPA (1994) currently lists an oral RfD for antimony from the LOAEL of 5 ppm antimony (adjusted as 0.4 mg/kg/day) in the drinking water of rats exposed for their lifetimes (Schroeder et al., 1970). This treatment was associated with reduced longevity in both sexes and blood biochemical alterations in males. Application of an uncertainty factor of 1000 resulted in an RfD of 4E-4 mg/kg/day.

The inhalation RfC for antimony is currently under review.

Based on weight of evidence, U.S. EPA (1987) classified antimony as Group D, not classifiable as to human carcinogenicity.

The proposed (U.S. EPA, 1994) MCLG for antimony is 0.003 mg/L, based upon a DWEL of 0.015 mg/L.

References:

Chulay, J.D., H.C. Spencer and M. Mugambi. 1985. Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). Am J Trop Med Hyg. 34: 702-709.

Gerber, G.B., J. Maes and B. Eykens. 1982. Transfer of antimony arsenic to the developing organism. Arch Toxicol 49: 159-168.

Crecelius, E.A. 1975. The geochemical cycle or afsenic in Lake Washington and its relation to other elements. Limnol Oceanogr. 20(3): 441-451

Moskalev, Y.I. 1959. Materials on the distribution of radioactive antimony. Med Radiol 4(3): 6-13.

Otto, G.F. and T.H. Maren. 1950. VI. Studies on the excretion and concentration of antimony in blood and other tissues following the injection of trivalent and pentavalent antimonials into experimental animals. Am J Hyg. 51: 370-385.

Potkonjak, V. and M. Pavlovich. 1983. Antimoniosis: A particular form of pneumoconiosis. I Etiology, Clinical and X-ray Findings. Int Arch Occup Environ Health. 51: 199-207.

Ragaini, R.X., H.R. Ralston and N. Roberts. 1977. Environmental trace metal contamination in Kellog, Idaho near a lead smelting complex. Environ Sci Technol. 11: 773-781.

Rompp. 1979. Chemie-Lexikon, Vol. 1. Stuttgart: Franckh 'sche Verlag Shandlung, p. 237 FF.

Rowland, H.A. K. 1971. Mathematical methods in research in tropical medicine. Ind Rev Trop Med. 4: 175-238.

Rugemalila, J.B. 1980. Fatal stibocaptate toxicity. East Afr Med J. 57: 720-722.

Schroeder E.F., F.A. Rose and H. Mast. 1946. Effect of antimony on the electrocardiogram. Am J Med Sci. 212: 697-706.

Schroeder, H.A., M. Mitchener and A.P. Nason. 1970 Zirconium, niobium, antimony, vanadium and lead in rats: life term studies. J Nutr. 100: 59-68.

U.S. EPA. 1987. Health Effects Assessment for Antimony. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington DC.

U.S. EPA. 1994. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Attachment II.

Risk Assessment Issue Paper for:
Provisional RfD for Cobalt (CASRN 7440-48-4)

Cobalt has been found to stimulate the production of red blood cells in humans and, therefore, has been used as a treatment for anemia. In 12 anemic, anephric patients undergoing dialysis, treatment with 0.18 mg cobalt/kg/day as cobalt chloride for 12 weeks resulted in a significant rise in hemoglobin (Duckham and Lee, 1976). Taylor et al. (1977) reported similar effects in 8 anephric patients treated with 0.16-0.32 mg cobalt/kg/day as cobalt chloride for 12-32 weeks. In both studies, hemoglobin levels returned to pre-treatment levels following the cessation of treatment. Similar effects were reported in nonanemic humans and animals (Davis and Fields, 1958; Krasovskii and Fridlyand, 1971). Reversible polycythemia was reported in 6 normal male subjects following treatment with 1 mg cobalt/kg/day as cobalt chloride for 25 days (Davis and Fields, 1958). In normal rats, treatment with 0.5 mg cobalt/kg/day, but not 0.05 mg/kg/day, as cobalt chloride resulted in polycythemia and an increase in hemoglobin (Krasovskii and Fridlyand, 1971). An increase in hematocrit and hemoglobin levels was not observed, however, in pregnant women treated with 0.5-0.6 mg cobalt/kg/day for 90 days in an attempt to alleviate the anemia often found during pregnancy (Holly, 1955).

Much of the oral data in humans deals with the cardiomyopathy seen in people who drank large quantities of beer containing cobalt chloride (used to stabilize the foam) (Alexander, 1969, 1972; Morin et al., 1971). The people ingested 0.04-0.14 mg cobalt/kg/day (approximately 8-30 pints of beer daily) over a period of years (Alexander, 1969, 1972; Morin et al., 1971). The cardiomyopathy in the beer-drinkers, termed "beer-cobalt cardiomyopathy", was fatal to 43% of the subjects within several years, with approximately 18% of these deaths occurring within the first several days. The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of the beer-cobalt cardiomyopathy was much more abrupt. The practice of adding cobalt to beer to stabilize the foam has been discontinued. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac and hepatic damage from alcohol abuse. Treatment of both pregnant and nonpregnant anemic patients with comparable or much higher doses of cobalt (0.09-1 mg cobalt/kg/day) did not result in effects on the heart (Duckham and Lee, 1976; Davis and Fields, 1958; Holly, 1955; Taylor et al., 1977).

Cobalt has been found to be a sensitizer in humans. Individuals are sensitized following dermal or inhalation exposure, but flares of dermatitis may be triggered following

---

cobalt ingestion. One study was located that orally challenged cobalt-exposed workers in order to assess sensitization (Veien et al., 1987). In this study, several patients with eczema of the hands were challenged orally with 1 mg cobalt (0.014 mg cobalt/kg/day as cobalt sulfate) in tablet form once per week for 3 weeks and 28/47 patients had a flare of dermatitis following the oral challenge (Veien et al., 1987). Forty-seven patients had positive patch tests to cobalt (13 to cobalt alone and 34 to nickel and cobalt) and 7 of the 13 patients that patch tested positive to cobalt reacted to the oral challenge. Using both the oral challenge and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure levels associated with sensitization to cobalt following inhalation or dermal exposure were not established.

Interrelationships have been found to exist between cobalt and nickel sensitization (Bencko et al., 1983; Rystedt and Fisher, 1983; Veien et al., 1987). In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al., 1985). Therefore, it is possible that in people sensitized by nickel, exposure to cobalt may result in an allergic reaction. The elicitation of an allergic response in cobalt-sensitized workers was considered for the derivation of an oral RfD. An oral RfD was not derived because a NOAEL for the elicitation of the allergic response in humans was not defined and, because interrelationships exist between cobalt and nickel sensitization, people sensitized by nickel may have an allergic reaction following cobalt exposure. Consequently, it is impossible to certify that an RfD based on this effect would provide sufficient protection for sensitive individuals.

Three studies were located examining the developmental effects of orally administered cobalt (given as cobalt chloride) in rodents (Domingo et al., 1985; Paternain et al., 1988; Seidenberg et al., 1986). Domingo et al. (1985) treated pregnant female rats to 5.4 to 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21. Fetal effects included stunted growth of the pups at 5.4 mg cobalt/kg/day and decreased survival at 21.8 mg cobalt/kg/day. These effects occurred at levels that were maternally toxic (authors did not specify the effects), therefore, the effects may be a result of maternal toxicity and not cobalt treatment. No teratogenic effects were reported.

No significant effects on fetal growth or survival were found in rats exposed to 6.2 to 24.8 mg cobalt/kg/day during gestation days 6-15 (Paternain et al., 1988), although a nonsignificant increase in the incidence of stunted fetuses was found in the animals treated with 12.4 or 24.8 mg cobalt/kg/day. Maternal effects, however, including reduced body weight and food consumption and altered hematological parameters, were reported. No fetal effects were reported in mice exposed to 81.7 mg cobalt/kg/day during gestation days 8-12 (Seidenberg et al., 1986), but a significant decrease in maternal weight was found.

Several studies reported testicular degeneration and atrophy in rats exposed to 5.7 to 30.2 mg cobalt/kg/day as cobalt chloride for 2-3 months in the diet or in the drinking water

(Corrier et al., 1985; Domingo et al., 1984; Mollenhauer et al., 1985; Nation et al., 1983; Pedigo et al., 1988).

Given the database, the most sensitive indicators of cobalt toxicity following oral exposure are the increase in hemoglobin in both humans and animals, and the elicitation of dermatitis in sensitized individuals.

An alternative approach was likewise evaluated based on the hematological effects of cobalt treatment (increase in hemoglobin) in anemic dialysis patients (Duckham and Lee, 1976). The results of this study are supported by a similar study in anephric patients (Taylor et al., 1977). Hematological effects of cobalt were also found in studies in normal humans (Davis and Fields, 1958) and rats (Krasovskii and Fridlyand, 1971) indicating that the effect is not limited to anephric individuals. The data of Davis and Fields (1958) reported hemoglobin increase of 6-11 % over "normal" in "normal" volunteers given 0.96 mg cobalt/kg/day as cobaltous chloride. However, the data of Duckham and Lee (1976) describes a case of refractory anemia in patients with chronic renal failure that upon treatment with 0.18 mg cobalt/kg/day for 12 weeks responded favorably. The patients hemoglobin levels were increased to levels at or near low "normal" clinical levels from levels clinically described as anemic. The anemia recurred following cessation of treatment. Thus, this effect of cobalt administration in the Duckham and Lee (1976) study (and likewise that of Taylor et al., 1977) cannot be termed adverse, but are actually clinically beneficial to patients with renal disease. Consequently, these data cannot be used to derive an oral RfD.

The only known nutritional, but vital function of cobalt is as a cofactor of vitamin B_{12}. In humans, vitamin B_{12} is derived from bacterial synthesis and therefore, cobalt is essential for animal species, such as ruminants, that depend totally on their bacterial flora for vitamin B_{12}. There is no evidence that the intake of cobalt is ever limiting in the human diet, and therefore no RDA is deemed necessary for cobalt (NRC, 1989). It should be noted that the average daily intake of cobalt in humans ranges from approximately 0.002-0.008 mg cobalt/kg/day in adults (0.16-0.58 mg cobalt/day ÷ 70 kg; Tipton et al., 1966; Schroeder et al., 1967) and 0.01-0.06 mg cobalt/kg/day in children (0.3-1.77 mg cobalt/day ÷ 28 kg; NRC, 1989; Murthy et al., 1971). Murthy et al. (1971) indicated that the children in this study ranged in age from 9-12 years. Using the average weight of 28 kg for children aged 7-10 years (NRC, 1989), the average daily intake for the children in this study ranged from 0.01-0.06 mg/kg/day. If the default adult weight of 70 kg is used with the Murthy data, then the range of intake would be from 0.004-0.025 mg/kg/day.

The effects of chronic occupational exposure to cobalt on the respiratory system are well documented. Cobalt has been found to be the etiologic agent in hard metal disease. The observed effects include respiratory irritation, wheezing, asthma, pneumonia and fibrosis and have been found to occur at exposure levels ranging from 0.003 to 0.893 mg cobalt/m^3

---

over a period of 2-17 years (Davison et al., 1983; Demedts et al., 1984; Kusaka et al., 1986a,b; Raffn et al., 1988; Shirakawa et al., 1988; Sprince et al., 1988).

Studies have implicated cobalt as a sensitizer in humans. Although the minimum exposure level associated with cobalt sensitization has not been determined, work-related asthma was found in hard metal workers who were occupationally exposed (for greater than 3 years) to levels of cobalt ranging from 0.007 to 0.893 mg cobalt/m^3 (Shirakawa et al., 1988). Given the database, the most sensitive indicators of cobalt toxicity by inhalation exposure are the effects on the respiratory system in both humans and animals and allergic responses in cobalt-sensitized individuals.

The data described above does not identify a single study, animal or human, that could be used to properly derive an oral RfD. In unusual circumstances, i.e., excessive beer drinking or through occupational sensitization, cobalt has been shown to manifest toxicological symptomatology. However, these reports provide inadequate data on which to derive an RfD. Furthermore, use of inhalation data to derive an oral RfD is precluded due to portal of entry effects. It is apparent that the upper range of average intake for children (0.06 mg/kg/day) is below the levels of cobalt needed to induce polycythemia in both renally comprised patients (0.18 mg/kg/day) and normal patients (0.96 mg/kg/day).

Therefore, in lieu of an oral RfD for cobalt and given the ubiquitous nature of cobalt and the relatively well characterized intake of cobalt in food, it is recommended that the intake levels described above be used as guidance for oral exposure to cobalt.

References:

Alexander, C.S. 1969. Cobalt and the heart. Ann. Int. Med. 70: 411-413.

Alexander, C.S. 1972. Cobalt-beer cardiomyopathy: A clinical and pathologic study of twenty-eight cases. Am. J. Med. 53: 395-417.

Bencko, V., V. Wagner, M. Wagnerova, et al. 1983. Immuno-biochemical findings in groups of individuals occupationally and non-occupationally exposed to emissions [sic] containing nickel and cobalt. J. Hyg. Epidemiol. Microbiol. Immunol. 27: 387-394.

Corrier, D.E., H.H. Mollenhauer, D.E. Clark, et al. 1985. Testicular degeneration and necrosis induced by dietary cobalt. Vet. Pathol. 22: 610-616.

Davis, J.E and J.P. Fields. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc. Soc. Exp. Biol. Med. 37: 96-99.

Davison, A.G, P.L. Haslam, B. Corrin, et al. 1983. Interstitial lung disease and asthma in hard-metal workers: Bronchoalveolar lavage, ultrastructural and analytical findings and results of
bronchial provocation tests. Thorax. 38: 119-128.

Demedts, M., B. Gheysens, J. Nagels, et al. 1984. Cobalt lung in diamond polishers. Am. Rev. Respir. Dis. 130: 130-135.

Domingo, J.L, J.M. Llobet and R. Bernat. 1984. A study of the effects of cobalt administered orally to rats. Arch. Farmacol. Toxicol. 10: 13-20.

Domingo, J.L, J.L. Paternain, J.M. Llobet, et al. 1985. Effects of cobalt on postnatal development and late gestation in rats upon oral administration. Rev. Esp. Fisiol. 41: 293-298.

Duckham, J.M. and H.A. Lee. 1976. The treatment of refractory anemia of chronic renal failure with cobalt chloride. Q. J. Med. 178: 277-294.

Holly, R.G. 1955. Studies on iron and cobalt metabolism. J. Am. Med. Assoc. 158: 1349-1352.

Krasovskii, G.N. and S.A. Fridlyand. 1971. Experimental data for the validation of the maximum permissible concentration of cobalt in water bodies. Hyg. Sanit. 36: 277-279.

Kusaka, Y., K. Yokoyama, Y. Sera, et al. 1986a. Respiratory disease in hard metal workers: An occupational hygiene study in a factory. Br. J. Ind. Med. 43: 474-485.

Kusaka, Y., Y. Ishikawa, T. Shirakawa, et al. 1986b. Effect of hard metal dust on ventilatory function. Br. J. Ind. Med. 43: 486-489.

Lammintausta, K., O.P. Pitkanen, K. Kalimo, et al. 1985. Interrelationship of nickel and cobalt contact sensitization. Cont. Dermat. 13: 148-152.

Mollenhauer, H.H., D.E. Corrier, D.E. Clark, et al. 1985. Effects of dietary cobalt on testicular structure. Virchows Arch. B. Cell Pathol. Incl. Mol. Pathol. 49: 241-248.

Morin, Y., A. Tetu and G. Mercier. 1971. Cobalt cardiomyopathy: Clinical aspects. Br. Heart J. 33: 175-178.

Murthy, G.K., U. Rhea and J.T. Peeler. 1971. Levels of antimony, cadmium, chromium, cobalt, manganese, and zinc in institutional total diets. Environ. Sci. Technol. 5: 436-442.

Nation, J.R, A.E. Bourgeois, D.E. Clark, et al. 1983. The effects of chronic cobalt exposure on behavior and metallothionein levels in the adult rat. Neurobehav. Toxicol. Teratol. 5: 9-15.

NRC (National Research Council). 1989. Recommended Daily Allowances. Tenth edition. Subcommittee on the Tenth Edition of the RDAs. Food and Nutrition Board.

Paternain, J.L., J.L. Domingo and J. Corbella. 1988. Developmental toxicity of cobalt in the rat. J. Toxicol. Environ. Health. 24: 193-200.

Pedigo, N.G, W.J. George and M.B. Anderson. 1988. Effects of acute and chronic exposure to cobalt on male reproduction in mice. Repro. Toxicol. 2: 45-53.

Raffn, E., S. Mikkelsen, D.G. Altman, et al. 1988. Health effects due to occupational exposure to cobalt blue dye among plate painters in a porcelain factory in Denmark. Scand. J. Work Environ. Health 14:378-384.

Rystedt, I. and T. Fischer. 1983. Relationship between nickel and cobalt sensitization in hard metal workers. Cont. Dermat. 9: 195-200.

Schroeder, H.A, A.P. Nason and I.H. Tipton. 1967. Essential trace elements in man: cobalt. J. Chronic. Dis. 20: 869-890.

Seidenberg, J.M, D.G. Anderson and R.A. Becker. 1986. Validation of an in vivo developmental toxicity screen in the mouse. Teratogen. Carcinogen. Mutat. 6: 361-374.

Shirakawa, T., Y. Kusaka, N. Fujimura, et al. 1988. The existence of specific antibodies to cobalt in hard metal asthma. Clin. Allergy. 18: 451-460.

Sprince, N.L., L.C. Oliver, E.A. Eisen, et al. 1988. Cobalt exposure and lung disease in tungsten carbide production: A cross-sectional study of current workers. Am. Rev. Respir. Dis. 138: 1220-1226.

Taylor, A., V. Marks, A.A. Shabaan, et al. 1977. Cobalt induced lipaemia and erythropoiesis. Dev. Toxicol. Environ. 1: 105-108.

Tipton, I.H., P.L. Stewart, P.G. Martin. 1966. Trace elements in diets and excreta. Health Phys. 12: 1683-1689.

Veien, N.K., T. Hattel, O. Justesen, et al. 1987. Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. Acta. Derm. Venereol. 67: 321-325.